MARIJUANA AS MEDICINE: WHERE HAVE WE BEEN, WHERE ARE WE NOW, AND WHERE ARE WE HEADING?

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CE Breakfast

December 14, 2014

Proposed Objectives

- Describe Basic Pharmacology & Uses of Marijuana
- Highlight Notable History of Marijuana Laws in the United States and Worldwide
- Explain Major Differences & Similarities between Maryland's "Medical Marijuana" (MMJ) Law and Other States
- Summarize Maryland's MMJ Law & Proposed Regulatory Frame-work
- Describe the Ongoing Role of the Natalie M. LaPrade Medical Marijuana Commission

CANNABIS PHARMACOLOGY

Endocannabinoid System

- Regulatory system in most animals to promote Homeostasis
  - Ex. Autophagy or apoptosis
  - Ex. Anti-inflammatory at injury sites
- Brain, organs, connective tissues, glands, and immune cells
  - CB1 predominantly present in the nervous system. Also connective tissues, gonads, glands, and organs
  - CB2 predominantly found in the immune system and its associated structures
  - No receptors in the brain stem = no respiratory & cardiac depression
- Anandamide, 2-arachidonoylglycerol (2-AG)
- Endocannabinoid-synthesizing and degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)

http://norml.org/library/item/introduction-to-the-endocannabinoid-system. Accessed December 8, 2014

Concentrations of CB_1 receptors

Basal Ganglia[1]
Movement

Cerebral Cortex[1]
Higher cognitive function

Cerebellum[1]
Movement

Hypothalamus[2]
Appetite

Hippocampus[1]
Learning, memory, stress

Medulla[3,4]
Nausea/vomiting, chemoreceptor trigger zone (CTZ)

Spinal Cord[1]
Peripheral sensation including pain

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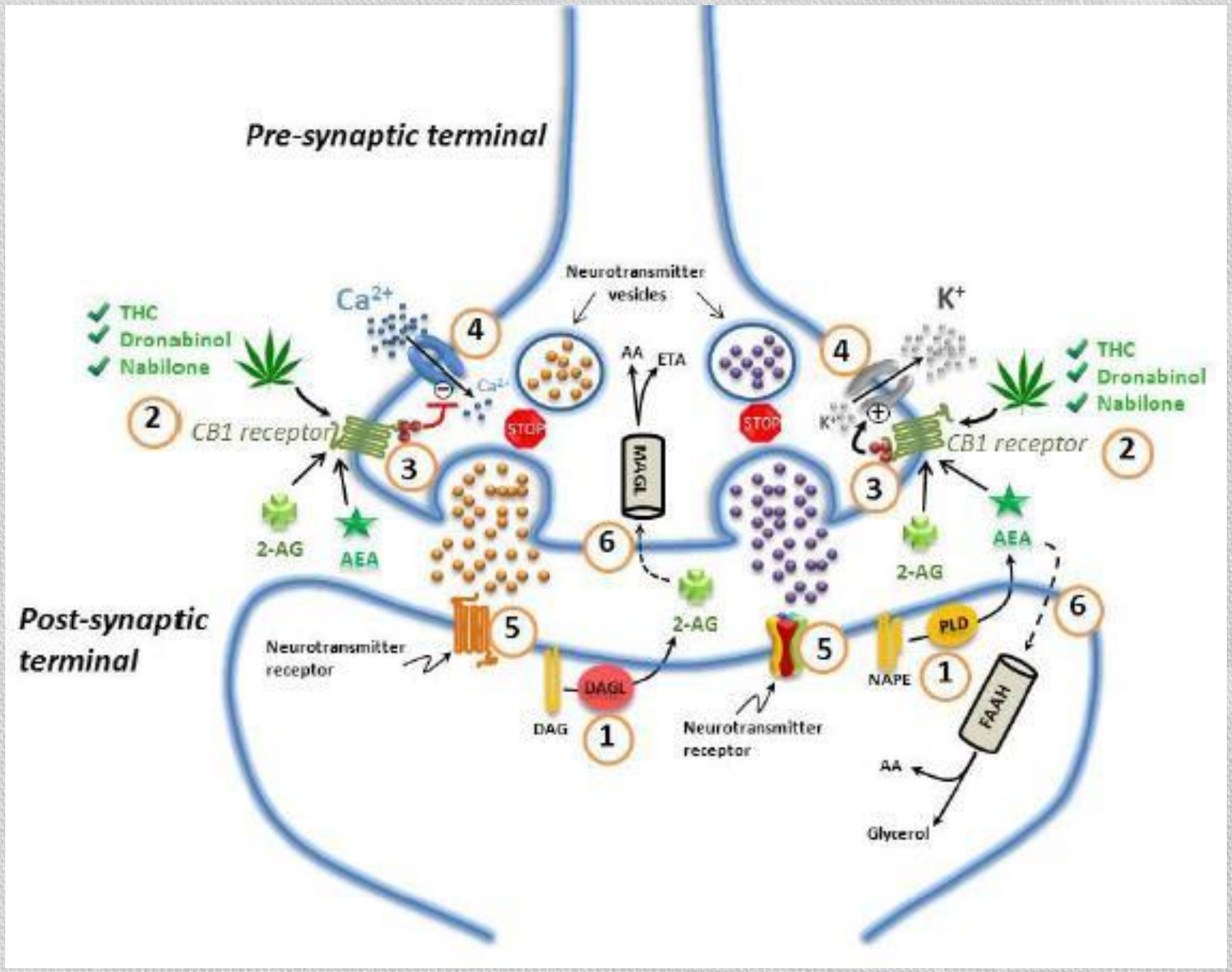

Pre-synaptic terminal
Post-synaptic terminal
THC
Dronabinol
Nabilone
CB1 receptor
2-AG
AEA
Ca2+
Neurotransmitter vesicles
AA
ETA
MAGL
STOP
K+
Neurotransmitter receptor
DAGL
DAG
PLD
NAPE
FAAH
Glycerol
1
2
3
4
5
6

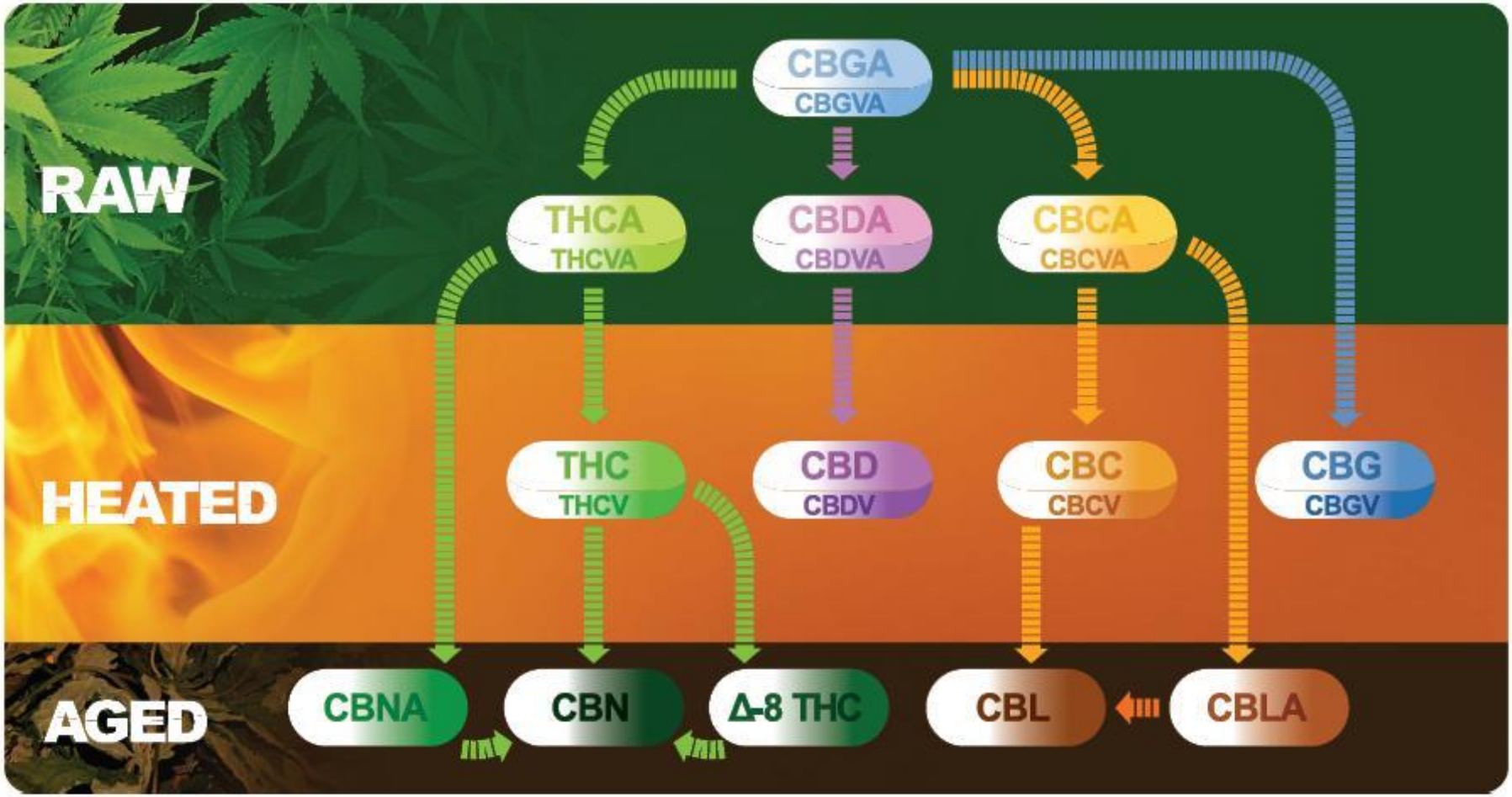
Exogenous Cannabinoids

- Phytocannabinoids – THC, CBD, and many others
  - Cannabis sativa, indica, ruderalis
  - Echinacea purpura (non-psychoactive)
  - Antioxidant protection from UV damage, Consumption deterrent
- Synthetic Cannabinoids
  - Dronabinol (Marinol)
  - Nabilone (Cesamet)
- Marketed Extracts
  - Nabiximols (tetranabinex, nabidiolex) (Sativex) ~50/50 THC/CBD Spray
  - Cannabidiol (Epidiolex) 98% pure CBD Spray

http://norml.org/library/item/introduction-to-the-endocannabinoid-system. Accessed December 8, 2014

UNDERSTANDING MEDICAL CANNABIS

Cannabinoids and Their Relationships



Steep Hill Halent

elemental wellness

Indications

- Dronabinol – cancer related nausea/vomiting, AIDS related weight loss
- Nabilone – cancer related nausea/vomiting
- Nabiximols
  - Multiple Sclerosis – spasticity, neuropathic pain
  - Cancer – moderate-severe, opioid-resistant chronic pain
- Cannabis
  - Trials – same indications as above, HIV-associated mood & insomnia, various chronic & neuropathic pain etiologies
- Epidiolex
  - NYU Seizure Trial in Dravet Syndrome initial data
  - ~30% reduction in seizure frequency
  - >50% reduction in 39% of patients

Pre-clinical & Anecdotal Indications

- Bladder dysfunction
- Amyotrophic Lateral Sclerosis
- Epilepsy
- Osteo & Rheumatoid arthritis, Fibromyalgia, Osteoporosis
- Glaucoma, Asthma, Hypertension
- Psychiatric Disorders including PTSD & ADD
- Alzheimer's Disease
- Movement Disorders (Parkinson's, Huntington's, Tourette's)
- Gastrointestinal Disorders
- Possible Anti-cancer effects
- Possible Anti-atherosclerotic effects

Dosing

- Highly individualized
  - Low < 7mg THC
  - Med 7-18mg THC
  - High > 18mg THC
- Multiple Dosage Forms
  - Inhaled – smoking, vaporization
  - Oral – Foods, butter, teas
  - Sublingual – oils, tinctures, sprays
  - Rectal, Topical (compresses, creams, ointments), IV
- Oral requires ~2.5 times inhaled weight for similar effect
- Majority use 10-20 grams per week for medical purposes
- "There is virtually no information in the peer-reviewed scientific or medical literature concerning the effects of varying CBD to THC ratios in the treatment of different medical disorders." – Health Canada

Table 2: Relationship between THC Percent in Plant Material and the Available Dose (in mg THC) in an Average Joint

% THC	mg THC per 750 mg dried plant material* ("average joint")
1	7.5
2.5	18.75
5	37.5
10†	75†
15	112.5
20	150
30	225

* *WHO average weight*

Drug Interactions

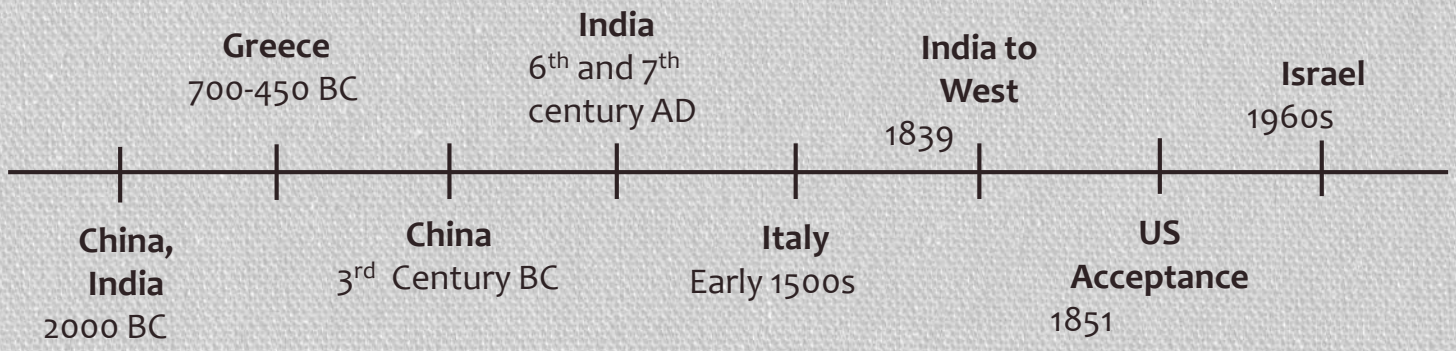
- THC is metabolized by CYP3A4, 2C9, & 2C19
- THC, CBD, & CBN inhibit 1A1, 1B2, 1A2 & P-gp (in vitro)
- CYP2C9
  - TCAs (tachycardia, delirium)
  - SSRIs (mania)
- CYP3A4
  - Protease inhibitors
  - Sildenafil (myocardial infarction & pulmonary hemorrhage)
- Warfarin – increased INR
- CNS Depressants – additive depressant effects

Adverse Effects

- Most Common
  - Increased heart rate, High feeling, decreased alertness, body sway, dizziness
- Carcinogenesis & mutagenesis
- Respiratory Tract
- Immune System
- Reproductive & Endocrine Systems
- Cardiovascular
- Gastrointestinal, Liver
- CNS
  - Cognition – Impairment, Memory loss
  - Psychomotor – Drowsiness, Dizziness, Ataxia, Appetite
  - Psychiatric – Intoxication, Addiction, Panic, Anxiety, Euphoria

A “BRIEF” HISTORY OF CANNABIS AND ITS LAWS AROUND THE WORLD

Timeline of Significant Events



Oldest Marijuana Known

- Marijuana used since 2000 BC in China and India
- 2700-year-old marijuana found in a Xinjiang, China tomb in 2008
  - 789 grams of dried cannabis with relatively high THC content
  - Likely meant to be used by shaman in the afterlife
  - Still looked green but had lost the “marijuana aroma”
- 大麻 = marijuana. Literal translation = “Big Numbness”

Chronicle of Medical Use

- Greece, 700-450 BC
  - Used for GI disorders
- China, 300 BC and India, 400-500 AD
  - Used for headaches
- Italy, 1500 AD
  - Opium tinctures for pain developed & used for centuries
- England, 1824 – Culpeper's Complete Herbal
  - Used for GI, headaches, gout, hip pain
- Ireland, 1839 – William O'Shaughnessy
  - Rheumatism & Infantile Convulsions

1839 – 1941

- Queen Victoria used for menstrual cramps
- 100s of studies led to many uses including migraine relief & appetite stimulation
- 1851 – Added to the U.S. Pharmacopoeia as a medical compound
- 1915 – Johns Hopkins' Sir William Osler – "Cannabis indica is probably the most satisfactory remedy for migraines"
- 1937 – Marijuana Tax Act banned Cannabis in the U.S.
  - Unreliable potency, quality control, common recreational use by "lazy" migrant workers, preference for opioids, & undesirable side effects
  - Criminalized against the advice of the American Medical Association
- 1941 – Removed from the U.S. Pharmacopoeia

1961 U.N. Single Convention on Narcotic Drugs

- 97 countries represented in Geneva, Switzerland
- 61 countries signed
- Resolutions included, *All countries* "should do everything in their power to combat the spread of the illicit use of drugs"
- Article 28 included, "The Parties shall adopt such measures as may be necessary to prevent the misuse of, and illicit traffic in, the leaves of the cannabis plant."
- 1970 Comprehensive Drug Abuse, Prevention & Control Act
  - Classified marijuana as CI and halted marijuana research in the U.S.
- As of 1990, cannabis is internationally classified as CI (so are opioids)

Pro-Cannabis Countries

- Official sources of cannabis – Netherlands, Canada, Israel, U.S.
- Approved pharmaceutical preparations – Canada, New Zealand, 8 European countries including Denmark, Germany, Spain, UK
- Traditional medicine use allowed – India (Ayurvedic)
- Decriminalized or Liberalized – Many European Union countries
- Full legalization – Uruguay, December 2013

Anti-Cannabis Countries

- Death penalty, Heavy Fines, Long Jail Sentences
  - Indonesia – death for drug trafficking
  - Iran – death for repeated cultivation & drug trafficking (> 5kg)
  - Malaysia – mandatory death penalty for drug trafficking (>200g)
  - Saudi Arabia – death for drug trafficking
  - Singapore – 20-30 years & 15 strokes of the cane for 330-500g; death for >500g
  - UAE – positive drug test, regardless of where consumed = prison. Death for trafficking
- Public Flogging & Deportation
  - Saudi Arabia

Netherlands

- Coffeeshops were Illegal but tolerated since 1980
- In 1998 the Dutch decided to establish a regulatory agency in accordance with article 28 of the Single Convention (same article the U.S. used to ban marijuana)
- March 1, 2000 the Office of Medicinal Cannabis (OMC) was founded
- January 1, 2001 the OMC was empowered as a national agency
  - Ensure constant quality which meets pharmaceutical standards
  - Establish an effective procedure for distribution
  - Prevent leakage to the criminal circuit (tracking procedure / recordkeeping)
  - Ensure availability of medicinal cannabis

Netherlands

- The OMC handles planning, contracting, licensing, quality control, import & export, and control / auditing of licensees
- Pharmacy dispensing legal & regulated since 2003
  - Counseling by physician & pharmacist
  - Quality issues addressed – pesticides, molds, bacteria, variability
  - Few choices limits confusion
    - 5 versus 1,000s
    - 2 flowers, 3 granulated products
  - Partial to full insurance coverage

Back to the United States

- Californians passed the first state law in 1996
- White House Office of National Drug Control Policy (ONDCP)
  - 1996 announced that participating physicians jeopardize their DEA registrations & their ability to participate in Medicare/Medicaid
  - Several physicians led by Marcus Conant, MD sued to block the action & won in North California District court in 2000 – Conant v. McCaffrey
  - 9th Circuit Court of Appeals affirmed in October 2002 – Conant v. Walters
  - Supreme Court denied the government's appeal in early 2003
- Department of Justice filed many civil & criminal suits against marijuana clubs & dispensaries but never challenged the validity of any state laws
- Many states received letters from U.S. Attorneys, including Delaware in February 2012

Background

- Supreme Court in 2005 ruled Congress has the authority to regulate or completely ban medical marijuana even if it remains intrastate
- 2009 "Ogden Memorandum" from the Department of Justice
  - "…should not focus federal resources in your States on individuals whose actions are in clear and unambiguous compliance with existing state laws providing for the medical use of marijuana"
- 2011 "Cole Memorandum"
  - "…never intended to shield [large-scale, privately-operated industrial marijuana cultivation centers] from federal enforcement action and prosecution, even where those activities purport to comply with state law

August 29, 2013 Updated Cole Memorandum

- Marijuana is still an illegal, Schedule 1 substance
- Enforcement of Marijuana Law is primarily the states' responsibility. As long as states show adequate willingness and ability to enforce their own laws, the Dept. of Justice is unlikely to intervene unless one of their core goals is violated, regardless of the scale of the operation

Recent National Developments

- February 14, 2014
  - Federal guidelines allow banks to provide financial services to legal marijuana sellers
  - Previously banks could face racketeering charges & be shut down
- May 30, 2014
  - U.S. House voted to block DEA's interference with MMJ operations
- Sept. 26, 2014 – "Charlotte's Web Medical Hemp Act of 2014" introduced
  - Representative Scott Perry of Pennsylvania
  - Would remove the term "marijuana" from therapeutic hemp & cannabidiol (CBD) strains
- December 9, 2014 – "Continuing Resolution and Omnibus Appropriations Bill" passed by both chambers of Congress
  - Passage will defund DEA operations against MMJ operations

FYI: Rescheduling Requirements

- 5 Requirements
  - Drug's chemistry must be known & reproducible
  - Adequate safety studies
  - Adequate and well-controlled efficacy studies
  - Accepted by qualified experts
  - Scientific evidence must be widely available
- OR!
  - Executive Order of the President
  - Congress

STATE MEDICAL MARIJUANA LAWS

MMJ Laws Around The Country

- Twenty three states and Washington, DC have enacted Medical Marijuana Laws
- 1 state has pending MMJ Legislation as of November 5, 2014

I. States with Legislation or Ballot Measures to Legalize Medical Marijuana

1 Pending Legislation or Ballot Measures

- Ohio

3 Passed Legislation in 2014

- Maryland
- Minnesota
- New York

15 Failed Legislation in 2014

- Florida
- Kansas
- Kentucky
- Maryland
- Minnesota
- Mississippi
- Missouri
- New York
- North Carolina
- Ohio
- Pennsylvania
- South Carolina
- Tennessee
- West Virginia
- Wisconsin

II. Pro-Medical Marijuana Legislation That Would Not Necessarily Legalize Its Use

1 **Pending Legislation or Ballot Measures**

- National

11 **Passed Legislation in 2014**

- Alabama
- Florida
- Iowa
- Kentucky
- Mississippi
- Missouri
- North Carolina
- South Carolina
- Tennessee
- Utah
- Wisconsin

7 **Failed Legislation in 2014**

- Alabama
- Florida
- Georgia
- Indiana
- Mississippi
- Nebraska
- North Carolina

Unique Legal Structure

- Laws must be crafted with features unusual to the practice of medicine
  - Anonymity of “prescribers” and patients
  - Various record confidentiality provisions
  - Caregivers
  - Compassion Centers
  - Avoidance of pharmacies (Connecticut is the exception)
  - Avoidance of the term “prescription”

Summary of State Laws

- *Laws vary widely from state to state*
- 1979 – 1991 Symbolic MMJ Laws
  - 5 states passed laws allowing "prescriptions"
  - Virginia, New Hampshire, Connecticut, Wisconsin, Louisiana
- Residency Required for Registration
  - 20 of 23 states require proof of state residency
  - Only Oregon accepts out of state applications
- Patient Registration: Mandatory vs. Voluntary
  - 11 of 23 states have voluntary registration
  - Registration protects from conviction but not arrest

Summary of State Laws

- Acceptance of Other State Registration
  - 6 of 23 states
- How Passed?
  - 12 State Legislatures, 10 Ballot Initiatives, 2 Constitution Amendments
- "CBD Only" States
  - Ten additional states passed "CBD Only" laws in 2014
  - Public opinion influenced by CNN's "Weed" series
  - 5 of the 10 nicknamed after children with Dravet Syndrome

Summary of State Laws

- Patient Registration Fees range from $0 - $200
- Possession Limitations
  - From 1 to 24 ounces per month
  - Cultivation of 4 to 24 plants, varying limits on mature plants & seedlings
- Home Cultivation
  - 15 of 23 states allow patient or caregiver cultivation
  - Arizona & Nevada – must live >25 miles from a dispensary at time of application
  - Massachusetts – must have a hardship waiver

Varying Features of Many State Laws

- Local bans including municipalities and college campuses
  - In May 2013, 200 California cities had banned dispensaries
- Provisions allow employers to more easily fire impaired employees
- Qualifying conditions
  - Narrowly-defined disease states
  - Lists of symptoms
  - No definition
- Oregon reclassified as C-II in 2010

Varying Features of Many State Laws

- Few attempt to define tolerable blood THC levels
- Taxation ranges from 0-25%
- Limitations on recommendations range from well-established Primary Care Physician to many “health care providers”
- Some limit inhalation route to vaporization only


MARYLAND

Maryland's Previous Laws

- 2003 Darrell Putman Compassionate Use Act (SB 502)
  - Allowed a "Medical Necessity" defense in court
  - If accepted the maximum fine for possession was $100
- 2011 Medical Marijuana – Affirmative Defenses – Maryland Medical Marijuana Model Program Workgroup Act (SB 308)
  - Clarified the 2003 law
  - Possession of ≤ 1 ounce for a debilitating condition determined in a bona-fide patient-physician relationship, and if not used in a public place
  - Created workgroup that led to the 2013 laws

Maryland's Previous Laws

- 2013 Medical Marijuana – Caregiver – Affirmative Defense Act (HB180)
- 2013 Medical Marijuana – Academic Medical Centers – Natalie M. LaPrade Medical Marijuana Commission Act (HB1101)
  - Authorized "Yellow Light" approach
  - Attempted to fill the research gap through closely monitored MMJ Compassionate Use programs
  - Regulations were ready for submission to the DHMH & the General Assembly's Joint Committee on Administrative, Executive, and Legislative Review (AELR) in February 2014 but…

Brief Decriminalization Sidebar

- 2014 Criminal Law – Possession of Marijuana – Civil Offense (SB364)
  - Possession of 10 grams or less
  - Child 16 or younger
    - Substance abuse class
    - First offense – $25 fine, 20 hours community service
    - Subsequent offenses - $100 fine, 40 hours community service
  - Adult
    - $100, $250, and $500 fines
    - 17-20 years old – Substance abuse class or addiction assessment & treatment

… Back to Medical Marijuana

- 2014 Medical Marijuana – Natalie M. LaPrade Medical Marijuana Commission Act (SB923)
- Passed by both houses on April 7, 2014
- Signed by Governor O'Malley on April 14, 2014
- Overhauled the medical marijuana program
- Retained the 2013 academic medical center research program

SB923 Major Points

- 3 New Cast Members Added
  - Original team of 12 – Secretary of DHMH representative, 3 physicians, 2 attorneys, 1 MMJ patient, 1 addiction expert, 1 chief of police, 1 hospice nurse, 1 research scientist, and 1 pharmacist
  - New members – 1 University of Maryland Extension representative, 1 horticulturalist, and 1 Comptroller representative
- Allows registration of certifying physicians
- Gives authorization to discuss MMJ with patients
- Removed AMC-only patient access limitation
- Reduced grower maximum from 25 to only 15

SB923 Major Points

- Authorizes dispensaries
- Authorizes all growers to also dispense
- Encourages high CBD strains, agricultural zone growers, multiple routes of administration, and minority ownership
- Provides legal protection to individuals and entities
- Disallows the commission from requiring reports of disciplinary actions against certifying physicians
- Allows patients of any age
- Provides limitations on where “smoking” can occur
- Outlines Commission responsibilities

Commission Responsibilities

- Approve certifying physicians
- Register patients
- Authorize new indications for MMJ use
- License, oversee, and inspect growers & dispensers
- Report to the General Assembly on youth marijuana use
- Research Veteran access to MMJ in Maryland
- Research MMJ taxation and impact on banking nationwide
- Authorize and oversee AMC research
- Draft Regulations
- Develop ranking scheme for grower & dispenser applications

The Regulations

- Overhaul of February 2014 regulations began May 2014, shortly after signing
- Adopted by the Commission on November 13, 2014
- Signed by Secretary Sharfstein on December 9, 2014
- 113 pages. Previous version had 43 pages.
- 28 sections. Previous version had 12 sections.

Notable Regulatory Sections

- New Condition Approval Process
- Quality Control by a Licensed Medical Marijuana Grower
- Complaints, Adverse Events, and Recall
- Inventory Control by Grower
- **Licensed Dispensary Clinical Director**
- Dispensing Medical Marijuana
- Fee Schedule

Other Regulatory Highlights

- No edibles at this time
- Symptoms, not diseases (except for Glaucoma & PTSD)
- Noone with a prior felony drug offense can be involved in growing or dispensing
- 30-day supply defined as “120 grams of usable marijuana”

What's Next?

- AELR → Final Publication
- The program begins!

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Question Time!